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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,086	02/07/2001	Rebecca Chinery	ATH 108 CON1	2259

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,086	CHINERY ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *4-17,20-22,24,25 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,18,19,23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/7/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-30 are currently pending.

Claims 1-3, 18, 19, 23 and 26 are under consideration.

Claims 4-17, 20-22, 24-25 and 27-30 are withdrawn from consideration.

Election/Restriction

1. Applicant's election without traverse of Group I (claims 1-3, 9, 10 and 16-30 in part) in Paper No. 9 (dated 7/24/03) is acknowledged.

2. Applicant's election of monosuccinic acid ester of probucol as the antioxidant species and carboplatin as the neoplastic species which reads on claim 1-3, 9-10, 18-19 and 23-30 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))

3. Applicant's further election without traverse of "hyperproliferative lesion" as the species of "a disorder of abnormal cell proliferation or solid growth" in the correspondence dated 11/21/03 which reads on claims 1-3, 18, 19, 23 and 26 is acknowledged.

4. Claims 4-17, 20-22, 24-25 and 27-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 2 and 26 are rejected under 35 U.S.C. 102(a,b) as being anticipated, or in the alternative obvious over Cheng et al., Cancer Letters (Shannon Ireland) (1990) vol. 51(3) pages 213-20..

Cheng et al. teach the ability of antioxidants (e.g. glutathione, vitamin E, vitamin C) to decrease cellular toxicity resulting from the administration of the "antineoplastic" (e.g. antiproliferative) cancer drug MGBG in yeast and mammalian cells (e.g. guinea pig keratinocytes) which suggests the concomitant (separately or in tandem) administration of the MGBG with these antioxidants in mammalian (e.g. human) drug therapy thus anticipating, or in the alternative rendering obvious the combined administration of these agents "to a host in need of treatment".

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

It is also noted that the prior art procedure inherently must enhance antitumor cytotoxicity and/or decrease resulting toxicity because the same protein is applied (e.g.

administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, of an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

8. Claims 1-3 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Cheng et al. teach the ability of antioxidants (e.g. glutathione, vitamin E, vitamin C) to decrease cellular toxicity resulting from the administration of the "antineoplastic" (e.g. antiproliferative) cancer drug MGBG in yeast and mammalian cells (e.g. guinea pig keratinocytes) suggest the concomitant administration of the MGBG with these antioxidants in mammalian (e.g. human) drug therapy thus anticipating, or in the alternative rendering obvious the combined administration of these agents "to a host in need of treatment".

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined

composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

It is also noted that the prior art procedure inherently must (enhance antitumor cytotoxicity and/or decrease resulting toxicity) because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

Although teaching the use of antioxidants with the cancer drug MGBG to decrease toxicity, the Cheng et al. Reference differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize antioxidants with MGBG in order to "increase the therapeutic index of the antineoplastic agent" with a

reasonable expectation of success in light of the Cheng teaching of reduced MGBG toxicity utilizing antioxidants which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be administered to cause toxicity (e.g. "toxic dose" in the numerator) thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of MGBG with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity resulting in an increased therapeutic index.

9. Claims 1-2 and 26 are rejected under 35 U.S.C. 102(a,b) as being anticipated, or alternatively obvious over Ripoll et al., J. Urology (1986) Vol. 136(2) pages 529-531.

Ripoll et al. teach combining an antioxidant (e.g. vitamin E) with an antineoplastic drug (E.g. adriamycin (ADR): antiproliferative i.e. growth inhibiting tumor agent) in order to additively/synergistically enhance ADR's cytotoxicity while decreasing ADR induced side effects including toxicity for in vitro use (e.g. cancer cells in cell cultures) which anticipates or in the alternative renders obvious administration to a host in need of treatment e.g. in the treatment of cancer (e.g. prostatic) as suggested by the reference.

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined

composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

Additionally, it is also noted that the prior art procedure inherently must enhance antitumor cytotoxicity and/or decrease resulting toxicity because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

10. Claims 1-3 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ripoll et al. and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Ripoll et al. teach combining an antioxidant (e.g. vitamin E) with an antineoplastic drug (E.g. adriamycin (ADR): antiproliferative i.e. growth inhibiting tumor agent) in order to additively/synergistically enhance ADR's cytotoxicity while decreasing ADR induced side effects including toxicity for in vitro use (e.g. cancer cells in cell cultures) which

anticipates or in the alternative renders obvious administration to a host in need of treatment e.g. in the treatment of cancer (e.g. prostatic) as suggested by the reference.

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

It is also noted that the prior art procedure inherently must (enhance antitumor cytotoxicity and/or decrease resulting toxicity) because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

Although teaching the use of an antioxidant with the cancer drug ADR to decrease ADR's toxicity and enhance ADR's cytoxicity, the Ripoll et al. Reference

differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize an antioxidant with ADR in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in light of the Ripoll teaching of :

a. reducing ADR's toxicity which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be administered to cause toxicity (e.g. "toxic dose" in the numerator); and/or

b. enhancing antitumor agent cytotoxity thus lowering the therapeutic amount of antitumor agent needed

thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of ADR with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity and increase cytotoxicity of ADR resulting in an increased therapeutic index.

11. Claims 1-2, 23 and 26, and rejected under 35 U.S.C. 102(a,b) as being anticipated by Yasunaga et al. Archiv Fuer Japnishe Chirurgie (1983) Vol. 52 (5) pages 591-601.

Yasunaga et al. teach that antioxidants (e.g. vitamin E) not only acts as a free radical scavenger to prevent cytotoxicity (e.g. cardiotoxicity) generated from the administration of antineoplastic agents (e.g. ADR, mitomycin) which generate free radicals (E.g. see page 591) but

Yasunaga et al. further teach that "[T]umor growth were significantly inhibited by the treatment of ADR, MMC or 5FU, and further there was a tendency that the antitumor effects of these three agents were promoted by the coadministration of vitamin E from our studies in BALB/c mice implanted with Meth A tumor" ... "We have applied vitamin E clinical in cancer therapy and obtained good preliminary results in immunological studies similar to this experimental data". E.g. see results and page 600. Accordingly, the reference teaches that coadministration of antioxidants with antitumor (e.g. antineoplastic: antiproliferative) agents results in decreased toxicity generated by the antitumor agent with enhanced cytoxicity of the agent's antitumor activity when administered to "a host(e.g. mammal: mouse/human) in need of treatment". .

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

Additionally, it is also noted that the prior art procedure inherently must enhance antitumor cytotoxicity and/or decrease resulting toxicity because the same protein is

applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

12. Claims 1-3, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yasunaga et al. and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Yasunaga et al. teach that antioxidants (e.g. vitamin E) not only acts as a free radical scavenger to prevent cytotoxicity (e.g. cardiotoxicity) generated from the administration of antineoplastic agents (e.g. ADR, mitomycin) which generate free radicals (E.g. see page 591)

Yasunaga et al. further teach that "[T]umor growth were significantly inhibited by the treatment of ADR, MMC or 5FU, and further there was a tendency that the antitumor effects of these three agents were promoted by the coadministration of vitamin E from our studies in BALB/c mice implanted with Meth A tumor" ... "We have applied vitamin E clinical in cancer therapy and obtained good preliminary results in immunological

studies similar to this experimental data". E.g. see results and page 600. Accordingly, the reference teaches that coadministration of antioxidants with antitumor (e.g. antineoplastic: antiproliferative) agents results in decreased toxicity generated by the antitumor agent with enhanced cytoxicity of the agent's antitumor activity when administered to "a host(e.g. mammal: mouse/human) in need of treatment". .

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

Additionally, it is also noted that the prior art procedure inherently must (enhance antitumor cytotoxicity and/or decrease resulting toxicity) because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

Although teaching the use of an antioxidant with antitumor agents to decrease antitumor generated toxicity and enhance antitumor drug cytoxicity, the Yasunaga et al. Reference differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize an antioxidant with an antitumor agent in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in light of the Yasunaga teaching of :

a. reducing antitumor agent toxicity which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be administered to cause toxicity (e.g. "toxic dose" in the numerator); and/or

b. enhancing antitumor cytotoxity thus lowering the needed therapeutic amount of antitumor agent needed

thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of an antitumor agent with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity and increase cytotoxicity of the antitumor agent resulting in an increased therapeutic index.

13. Claims 1-2, 23 and 26 are rejected under 35 U.S.C. 102(a,b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Szczepanska et al. Eur. J. Haematology (1988) Vol. 40(1) pages 69-74.

Szczepanska teach that antioxidants (e.g. vit. E, vit C and thiourea) protect against cytotoxic adverse effects of chemotherapeutics from different classes (e.g. adriblastine, hydroxyurea, methotrexate, 5-fluorouracil, 6 mercaptopurine, etc.: see abstract) as shown in in vitro human blood experiments (e.g. see entire article, including abstract, table 1 and Discussion section) which were devised to " ... maintain the conditions of drug treatment close to those in vivo.." (See page 69 (right column).

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

It is also noted that the prior art procedure inherently must (enhance antitumor cytotoxicity and/or decrease resulting toxicity) because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease

toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

14. Claims 1-3, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szczepanska et al. and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Szczepanska teach that antioxidants (e.g. vit. E, vit C and thiourea) protect against cytotoxic adverse effects of chemotherapeutics from different classes e.g. adriblastine, hydroxyurea, methotrexate, 5-fluorouracil, 6 mercaptopurine, etc.: see abstract) as shown in in vitro human blood experiments (e.g. see entire article, including abstract, table 1 and Discussion section) which were devised to " ... maintain the conditions of drug treatment close to those in vivo.." (See page 69 (right column).

Accordingly, the reference provides a teaching of administering (together or consecutively) an antioxidant and an antitumor agent which would immediately envisage (e.g. anticipate) or alternatively render obvious administration of the combined composition *in vivo* (e.g. "to a host in need of treatment") or alternatively *in vitro* to treat a solid growth of abnormally proliferating cells. See e.g. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); MPEP 2131.02; MPEP 2144.08.

It is also noted that the prior art procedure inherently must (enhance antitumor cytotoxicity and/or decrease resulting toxicity) because the same protein is applied (e.g. administered) in the same way in the same amount. *In re Best*, 195 USPQ 430,433

(CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). For example, a reference teaching the administration consecutively, or in combination, an antineoplastic drug and an antioxidant for purposes of enhancing antineoplastic cytotoxicity to treat a tumor (e.g. "solid growth of abnormally proliferating cells") would inherently decrease toxicity where the type and amount of antioxidant administered to the same host for enhancing antineoplastic drug cytotoxicity is identical for that needed to decrease the antineoplastic drug toxic side effects (and vice versa), which is true in the present instance.

Although teaching the use of an antioxidant with antitumor agents to decrease antitumor generated toxicity and enhance antitumor drug cytoxicity, the Szczepanska reference differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize an antioxidant with an antitumor agent in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in light of the Szczepanska teaching of :
a. reducing antitumor agent toxicity which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be administered to cause toxicity (e.g. "toxic dose" in the numerator); and/or

b. enhancing antitumor cytotoxity thus lowering the needed therapeutic amount of antitumor agent.

thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of an antitumor agent with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity and increase cytotoxicity of the antitumor agent resulting in an increased therapeutic index.

15. Claims 2, 18 and 26 are rejected under 35 U.S.C. 102(a,b) as anticipated by Siveski-Iliskovic et al. Circulation Vol. 91, Issue 1 (Jan. 1995) pages 10-15.

Siveski-Iliskovic et al. teach coadministration (E.g. injection)e of probucol (e.g. antioxidant) with adriamycin (e.g. antineoplastic) in a mammal (e.g. rat) to treat solid growth of abnormally proliferating cells (e.g. a tumor) in order to protect against the toxic side effects of adriamycin.

16. Claims 2-3, 18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siveski-Iliskovic et al. and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Siveski-Iliskovic et al. teach coadministration (E.g. injection)e of probucol (e.g. antioxidant) with adriamycin (e.g. antineoplastic) in a mammal (e.g. rat) to treat solid growth of abnormally proliferating cells (e.g. a tumor) in order to protect against the toxic side effects of adriamycin.

Although teaching the use of an antioxidant with antitumor agents to decrease antitumor generated toxicity, the Siveski-Iliskovic et al. reference differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize an antioxidant with an antitumor agent in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in light of the Siveski-Iliskovic et al. teaching of :

reducing antitumor agent toxicity which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be administered to cause toxicity (e.g. "toxic dose" in the numerator) thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of an antitumor agent with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity of the antitumor agent resulting in an increased therapeutic index.

17. Claims 2, 18, 19 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siveski-Iliskovic et al. and Parthasarathy US Pat. No. 5,262,439 (11/93).

Siveski-Iliskovic et al. teach coadministration (E.g. injection)e of probucol (e.g. antioxidant) with adriamycin (e.g. antineoplastic) in a mammal (e.g. rat) to treat solid growth of abnormally proliferating cells (e.g. a tumor) in order to protect against the toxic side effects of adriamycin.

The Siveski-Iliskovic et al. reference differs from the presently claimed invention (e.g. claim 19) by teaching the unesterified antioxidant (e.g. probucol) instead of mono/di esters.

However, Parthasarathy teaches the benefits of employing water soluble antioxidant (e.g. probucol) mono/di esters instead of the unesterified e.g. more readily absorbed and administered intravenously. See e.g. abstract col. 1-2.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize water-soluble mono/di esterified antioxidants (e.g. probucol) in place of the corresponding unesterified Siveski-Iliskovic et al antioxidant in order to obtain the benefits thereof as taught by the Parthasarathy reference.

18. Claims 2, 23 and 26 are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Borch et al. US Pat. No. 5,035,878 (7/91)..

Borch et al. teaches administration (with or consecutively) of dithiocarbamates (e.g. antioxidant) to decrease toxicity (e.g. bone marrow/kidney etc.) of antineoplastic drugs (e.g doxorubicin, carboplatin etc.) for treatment of solid growth of abnormally

proliferating cells (e.g. tumors). See abstract; col. 1-3 (especially col 3 top); col. 6; claims.

19. Claims 2-3, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borch '878 and the American Heritage Dictionary of the English Language: 4th Ed. 2000 definition of "therapeutic index".

Borch et al. teaches administration (with or consecutively) of dithiocarbamates (e.g. antioxidant) to decrease toxicity (e.g. bone marrow/kidney etc.) of antineoplastic drugs (e.g doxorubicin, carboplatin etc.) for treatment of solid growth of abnormally proliferating cells (e.g. tumors). See abstract; col. 1-3 (especially col 3 top); col. 6; claims.

Although teaching the use of an antioxidant with antitumor agents to decrease antitumor generated toxicity, the Borch reference differs from the presently claimed invention by failing to *explicitly* teach "increase of the therapeutic index".

However, "therapeutic index" is defined (e.g. see American Heritage Dictionary) as "[T]he ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment".

One of ordinary skill in the art would be motivated to utilize an antioxidant with an antitumor agent in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in light of the Borch teaching of :

reducing antitumor agent toxicity which would thus decrease the therapeutic index (toxic dose/therapeutic dose is >1) by increasing the dose that needs to be

administered to cause toxicity (e.g. "toxic dose" in the numerator) thus increasing the therapeutic index.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize the combination of an antitumor agent with an antioxidant in order to "increase the therapeutic index of the antineoplastic agent" with a reasonable expectation of success in view of the decrease in toxicity of the antitumor agent resulting in an increased therapeutic index.

Relevant Publications:

1. Weijl et al. Cancer Treatment Reviews (July 1997) Vol. 23(4) pages 209-240.

2. Borch et al. US Pat. No. 5,294,430.

3. Cloos et al. Carcinogenesis (1996) Vol. 17 (2) pages 327-31.

4. Biosis AN: 1990:428349: Abstract of Hannemann et al., Archives of Toxicology (1990) Vol. 64 No. 5 pages 393-400.

5. Embase AN: 9227964: Abstract of Jaakkola et al., Anticancer Research (1992) Vol. 12(3) pages 599-606.

6. Chinery et al., Nature Medicine Vol. 3 No. 11 (Nov. 1997) pages 1233-1241.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
February 19, 2004